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RECORD OF ORAL HEARING

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES

*Ex parte* MICHAEL T. TRESE, GEORGE A. WILLIAMS,  
and MICHAEL K. HARTZER

Appeal 2009-007265  
Application 10/068,314  
Technology Center 3700

Oral Hearing Held: May 11, 2010

Before JOHN C. KERINS, STEVEN D.A. McCARTHY, and  
MICHAEL W. O'NEILL, *Administrative Patent Judges*.

APPEARANCES:

ON BEHALF OF THE APPELLANT:

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1           The above-entitled matter came on for hearing on Thursday, May 11,  
2   2010, commencing at 1:05p.m., at the U.S. Patent and Trademark Office,  
3   600 Dulany Street, Alexandria, Virginia, before Paula Lowery, Notary  
4   Public.

5   CLERK: Good afternoon, Calendar Number 44, Appeal No. 2009-007265,  
6   Mr. Goldstein.

7   JUDGE KERINS: We have reviewed the record and are generally familiar  
8   with the issue. We're happy to hear your argument.

9   MR. GOLDSTEIN: I'd like to very briefly walk you through several points.  
10  The claims are directed to a method of liquefaction, and in regard to a  
11  majority of the claims -- including the two dependent claims -- there's a 103  
12  rejection over a reference that's been referred to in the record as the  
13  ophthalmology reference.

14  If we look at that reference, and if you can indulge me and take a look at a  
15  few points within that reference, specifically on page 2 of the reference.

16  This reference talks about what their intended purpose was.

17  Under an article outlined, it notes that we believed that this, namely the use  
18  of plasmin with respect to treatment measurables in pediatrics, would allow  
19  less traumatic separation of the vitreous from the retina in the optic nerve  
20  head.

21  I wanted to highlight that that was the purpose, or the intended goal, of this  
22  study. On the following page, page 3, the last complete paragraph, the last  
23  sentence states: "In May, 1996 the first patient consent was obtained for the  
24  use of autologous plasmin only if the posterior vitreous detachment (PVD)  
25  could not be achieved safely by standard methods."

26  The following page goes to the procedure. The reason –

1 JUDGE MCCARTHY: Counsel, could you perhaps go into a little more  
2 detail as to what is meant by the detachment of the vitreous?

3 MR. GOLDSTEIN: Sure. I apologize it's after lunch and we're discussing  
4 this topic.

5 The vitreous of the eye is, basically, a gelatinous sack of material. Behind it  
6 is the rods and cones that create the inside of the eye, sort of forming a  
7 hemisphere that's connected to the optic nerve.

8 In a number of instances the vitreous -- actually, with age is the most  
9 common occurrence -- this sack of vitreous separates from the retina. Most  
10 of the time that happens gently. You're not even aware of it.

11 If there's an impact or some tearing, that's an occurrence where people sense  
12 either spider webs in their vision; or they'll notice sort of little things floating  
13 in their visual path.

14 You know, that's the common procedure. Again, it occurs with age. In  
15 some instances with trauma the same thing occurs.

16 A vitrectomy is the process by which the vitreous is actually removed.

17 Usually because there is damage or vulnerability to the retina behind it.

18 This particular reference, dealing with macular holes, is basically a trauma.

19 The children involved were in one way or another hit by a ball or something  
20 else to actually cause a region of the retina to, basically, detach and become  
21 separated.

22 The standard treatment for this is, basically, the vitreous is removed.

23 Everything is stabilized and actually a gas bubble, they call it a tamponade,  
24 is put into it for the gas bubble to push the detached portion of the retina  
25 back up against the optic nerve.

26 The patient then has to, basically, stay in a head-down position for a number

1 of weeks to keep that gas bubble pressing everything back into contact.  
2 The conventional problems with a vitrectomy is the vitreous is gelatinous  
3 and a lot of times it doesn't come out so nicely, especially in children where  
4 they haven't had the benefit of age to sort of loosen everything up.  
5 As a result, there tends to be a large bore needle and also a mechanical cutter  
6 with suction. So it's physically sort of scraping out the gelatinous material  
7 of the vitreous.

8 That's sort of the background from which the present invention arose.  
9 Namely, if you, in fact, do have to suck out the vitreous, the smaller the  
10 bore, the less complications associated with that; and if you can avoid  
11 mechanical abrasions --

12 The important thing I wanted to emphasize is the procedure that was  
13 involved only occurred after the PVD, posterior vitreous detachment, cannot  
14 be achieved safely by standard methods.

15 So the protocol did not even allow them to do what the claims are proposing,  
16 namely simply inject plasmin into an otherwise unchanged eye in an attempt  
17 to liquify it.

18 On page 4 of the reference, it goes through in a paragraph beginning "In the  
19 first patient," it talks about doing a complete mechanical vitrectomy with the  
20 removal of the vitreous, which appeared in this paragraph to say this seemed  
21 to be successful because of the presence of what appeared to be a Y spring.  
22 During the air/fluid exchange, which is this tamponade, that took place to  
23 push the macular hole back up against the back of the eye, it became  
24 apparent that the cortical vitreous was delaminated. So this was their  
25 instance that they could now go -- they had satisfied the consent form. They  
26 tried to do a classic or additional posterior vitreous detachment procedure,

1 and it didn't work. Now, they were within the consent actually trying to use  
2 the enzymes to actually help with this delamination.  
3 The subsequent paragraph goes on to say that after 15 minutes of the  
4 enzymes being present, they actually were able to -- "The remaining cortical  
5 vitreous was easily separated from the underlying neurosensory retina with a  
6 soft-tip cannula."  
7 Skipping one sentence, "This sheet of tissue is clearly separate from the  
8 cortical vitreous and had to be removed from the underlying neurosensory  
9 retina surrounding that macular hole with dissection."  
10 So, again, even with the use of the plasmin, the active enzymes to help with  
11 the delamination, they still had to do mechanical dissection to address this.  
12 Further in the same paragraph it states: "A standard plasmin vitrectomy was  
13 performed with the peeling of the posterior cortical vitreous using the  
14 technique described by Kelly and Wendell."  
15 So this reference, over which the two independent claims are rejected, I  
16 submit they cannot, in fact, teach liquefaction of the vitreous because  
17 practice -- the vitreous has already been removed before they began the  
18 introduction of the enzyme.  
19 JUDGE O'NEILL: Well, wasn't there some of the vitreous still left? I  
20 mean, that's why it's delaminated.  
21 MR. GOLDSTEIN: There was the cortical vitreous, in other words that's  
22 sort of the skin part of this gelatinous bag.  
23 JUDGE O'NEILL: So the vitreous -- it's a sphere, and there's an outer  
24 surface called the cortical vitreous, and then the vitreous itself?

1 MR. GOLDSTEIN: Yes, the vitreous is really just a gelatinous substance,  
2 and sometimes that substance actually forms a skin that adheres to the retina,  
3 which is normal.

4 The purpose of this paper and the problem they had here is the cortical  
5 vitreous was, basically, it's like a skin was attached to the retina.  
6 In the process of -- even with the enzyme, in the process of pulling it off,  
7 they noted that they removed some underlying neurosensory retina  
8 surrounding the hole. So they actually had to cut it free, even with the use of  
9 the enzyme.

10 JUDGE O'NEILL: So are you saying that the injection of .4 IUs did not  
11 even liquefy any part of the cortical vitreous? Is that what you're saying?  
12 Because they had to literally mechanically cut part of the retina out as well?

13 MR. GOLDSTEIN: That's right. They actually had to go in with a sharp  
14 dissection. They actually had to physically cut the material.

15 JUDGE KERINS: Counsel, doesn't that say they did that after they easily  
16 separated vitreous from the underlying retina?

17 It says: "In addition to the vitreous, a large sheet of the pre-retinal tissue  
18 was removed." It talks about that tissue being dissected.

19 MR. GOLDSTEIN: Yes, so the retinal tissue, the rods and cones, pulled  
20 away as well and had to be cut free.

21 JUDGE KERINS: But they had previously removed vitreous by the  
22 injection of the enzyme.

23 MR. GOLDSTEIN: Yes, the procedure detailed in here is initially they  
24 pulled out the volume of the vitreous. They thought they were done, but it  
25 appeared that the cortical vitreous, this skin-like layer, remained in contact  
26 with the retina.

1 They then injected the enzyme, and got separation, but in the process the  
2 retinal tissue also pulled away and had to be cut as well.

3 In other words --

4 JUDGE KERINS: Your claim is just directed to liquefaction of the vitreous.

5 MR. GOLDSTEIN: That's right.

6 JUDGE KERINS: And you're saying that didn't occur here?

7 MR. GOLDSTEIN: The vitreous wasn't in the eye when this even occurred.

8 JUDGE KERINS: It says there was remaining cortical vitreous, and that  
9 was after the mechanical procedure.

10 JUDGE MCCARTHY: Counsel, if I may, what do you mean in Claim 1 by  
11 vitreous body?

12 MR. GOLDSTEIN: With reference to Figure 1, I believe it's referencing 16,  
13 the vitreous humor, which is -- in other words it's the volume of the vitreous  
14 within the eye.

15 JUDGE MCCARTHY: So you had the volume of vitreous, then you have a  
16 cortical vitreous around the vitreous gel?

17 MR. GOLDSTEIN: The gel has a self containing skin or sheet around it that  
18 is in contact normally -- direct contact -- with the retina. As people age the  
19 cortical vitreous tends to pull away from it so you've got these gaps.

20 JUDGE MCCARTHY: So in a preferred embodiment of the subject matter  
21 of Claim 1, you would be liquefying the vitreous gel, but you would not be  
22 liquefying the cortical vitreous?

23 MR. GOLDSTEIN: That's right. In other words, the goal of the claim is to  
24 avoid having to take -- just as described in this prior reference -- to take out  
25 a mechanical cutter or any other type of process. To the extent that you're



1 applying suction, you're able to do it with a much finer bore needle which,  
2 obviously, creates less scar tissue and everything else.

3 In fact, it was the subject matter of Claims 26 through 28, which referred to  
4 the suctioning performed through a 25 or finer gauge instrument -- which is  
5 something that's not disclosed here -- where, in fact, it's a much larger bore  
6 needle. I believe a 20 gauge needle.

7 JUDGE O'NEILL: So the injection of the .4 IUs in the reference did not  
8 cause liquefaction of the cortical vitreous?

9 MR. GOLDSTEIN: That's correct. In other words, they had sucked it out  
10 previously.

11 JUDGE O'NEILL: But you're saying to us that the cortical vitreous is part  
12 of the vitreous, correct?

13 MR. GOLDSTEIN: It's an outer skin, if you will.

14 JUDGE O'NEILL: Inserting the .4 IUs, that didn't liquefy it? Did not  
15 liquefy the cortical vitreous at all?

16 MR. GOLDSTEIN: The vitreous humor, the vitreous body, was previously  
17 gone. What's left --

18 JUDGE O'NEILL: Is the skin.

19 MR. GOLDSTEIN: -- is the skin.

20 JUDGE O'NEILL: Now, they inserted .4 IUs and that .4 IUs -- it's your  
21 position that that .4 IUs did not cause any type of liquefaction?

22 MR. GOLDSTEIN: It caused delamination.

23 JUDGE O'NEILL: It caused delamination.

24 MR. GOLDSTEIN: There's no evidence that it actually caused it to lose it's  
25 long-range order.

26 JUDGE O'NEILL: Say that again. Long range what?

1 MR. GOLDSTEIN: In other words, a gel has a certain long-range order. A  
2 skin has a long-range order to it where the liquid --

3 JUDGE KERINS: Similar to a polymer.

4 MR. GOLDSTEIN: Exactly. The gel will retain the shape of the container  
5 it's made in, whereas water -- that's a terrible example.

6 Jello, if you take it out of the mold, will hold its shape with a little bit of  
7 jiggling; whereas a liquid, if you pour it out of its container, it has no  
8 inherent shape. No long-range order to it.

9 JUDGE MCCARTHY: So I take it then that it's your position that someone  
10 reading this article, at the time the subject matter was made, would have  
11 been able to glean from this article that .4 IUs of a plasmin would liquefy the  
12 vitreous gel?

13 MR. GOLDSTEIN: That's right. Firstly, because the gel wasn't even  
14 present when it was done based on their consent. It had been pulled out  
15 previously.

16 Also, if you've had a chance to review the numerous Declarations that were  
17 made of record, during the course of prosecution, the Examiner asked what  
18 was an excellent question which is: They're using .4 IUs, you're using .4  
19 IUs, what's the difference?

20 Those Declarations really speak to when this original paper was done. They  
21 were activating the plasmin, the actual active enzyme, from plasminogen  
22 with equal amounts of streptokinase.

23 What they discovered was the streptokinase and the plasminogen formed a  
24 complex that has much lower enzymatic activity than the plasmin itself.

25 When they lowered the amount of streptokinase they were introducing to  
26 activate the plasminogen to create the active plasmin, they discovered this

1 complex sort of catalytically converts plasminogen to plasmin. That was  
2 made of record to explain that difference.

3 JUDGE O'NEILL: Which Declaration explained that difference? We have  
4 three here: two from Hartzer and one from Gaffney.

5 MR. GOLDSTEIN: You actually have three from Hartzer, which is quite an  
6 accomplishment, and one from Gaffney.

7 Certainly Gaffney's Declaration speaks directly to that point, as does the first  
8 Declaration of Michael Hartzer. To be honest, all the Declarations are really  
9 very much focused on this point of trying to make a record that what they  
10 thought was plasmin, in fact, they had a small amount of plasmin and much  
11 more of this streptokinase plasminogen complex.

12 JUDGE MCCARTHY: Counsel, do any of the Declarations quantify how  
13 much the streptokinase plasminogen complex affects the activity?

14 MR. GOLDSTEIN: Yes, there's a very nice graph -- if you look in the  
15 Supplemental Declaration of Michael Hartzer, Paragraph 5. There's a bar  
16 graph that involves rapid vitreous viscosity.

17 So there they were sort of measuring the amount of time it took to suction  
18 out 1000 micro liters with a control with 1 IU of plasmin and 1 of  
19 streptokinase plasminogen complex.

20 So at the time the ophthalmology paper was written, they thought they had  
21 plasmin but, in fact, it was this complex.

22 JUDGE O'NEILL: Which paper are we talking about?

23 MR. GOLDSTEIN: I'm sorry, the ophthalmology paper, the prior reference.

24 JUDGE KERINS: So, Counsel, we have the ophthalmology paper that  
25 discusses the .4 IUs of plasmin enzyme. Based on the Declarations which  
26 say that was not accurately characterized as .4 IUs of plasmin --

1 MR. GOLDSTEIN: That's right.

2 JUDGE KERINS: -- what in these Declarants' testimony tells us how much  
3 plasmin was actually involved in the procedure used in the ophthalmology  
4 paper?

5 MR. GOLDSTEIN: The amount is roughly 12 percent of the total.

6 JUDGE KERINS: So that would be roughly .05 units?

7 MR. GOLDSTEIN: .05, yes. I'm looking for a citation for you.

8 JUDGE KERINS: I believe I saw that now that you've brought that to my  
9 attention.

10 MR. GOLDSTEIN: Okay.

11 JUDGE MCCARTHY: Is that the reason, Counsel, we end up with a lower  
12 limit on the range of plasmin in the claims?

13 MR. GOLDSTEIN: Practically, that was there to deal with some 112 issues;  
14 and, more than anything else, just to try to advance prosecution.  
15 Truthfully, I believe the claims are broader than the concentration limits or  
16 the volume limits for a couple of reasons.

17 One, they support the specification, and the other is that because it is an  
18 enzyme, enzymatic reactions -- I think a lot of the record reflects a  
19 concentration issue, which would be true of a small molecule  
20 pharmaceutical. But the enzyme -- less enzyme, apparently, just leads to a  
21 longer time to get to the same place.

22 JUDGE MCCARTHY: Counsel, how would the data that we had before us  
23 indicate that what was being done in the prior art article, or I should say the  
24 complex that was being used in the prior art article, did not have a plasmin  
25 unit within the less than .4 to .1 range?

26 MR. GOLDSTEIN: Oh, in terms of the concentration of it?

1 JUDGE MCCARTHY: Yes.

2 MR. GOLDSTEIN: Even if it did, even if the amounts are the same,  
3 because of what was actually taught in that reference, I submit one skilled in  
4 the art without -- after having performed a vitrectomy and just left the  
5 cortical vitreous that adhered to the retina, trying to liquefy the vitreous  
6 when it's practically already been mechanically suctioned out, I don't see  
7 how one skilled in the art could extend from something not being present to  
8 the enzyme being reactive with it.

9 JUDGE O'NEILL: I think you have really two main arguments. One is that  
10 the vitreous is already out, so the claim's not in that.

11 MR. GOLDSTEIN: That's right.

12 JUDGE O'NEILL: Your other argument is that the concentration of the  
13 plasmin enzyme in the reference does not fall within the range of .4 units to  
14 .1 unit.

15 MR. GOLDSTEIN: That's right. Once you consider the Declaration --

16 JUDGE O'NEILL: If you consider the Declaration.

17 MR. GOLDSTEIN: Right. If the Declarations are considered on their face,  
18 you know, again I believe the number is about 12 percent of the total was  
19 active plasmin.

20 JUDGE O'NEILL: Judge Kerins said about .05.

21 JUDGE KERINS: That's

22 Paragraph 3 of the Supplemental Declaration that has the 12 percent figure  
23 in it.

24 JUDGE MCCARTHY: Counsel, would you agree then that this prior art  
25 Trese article might suggest, to one of ordinary skill in the art, that injecting

1 .4 IUs or above of at least this streptokinase plasminogen complex could  
2 cause separation between the cortical vitreous and the retina?

3 MR. GOLDSTEIN: I certainly agree with that. I think they've shown that.  
4 There's also a statement copied in the Reply Brief from the Examiner's  
5 Answer that I thought is also quite relevant. I could read that into the  
6 record:

7 "The Applicant argues that a dose of 0.4 in the prior art references fails to  
8 teach liquefaction, which the Examiner disagrees with. Both prior  
9 references teach plasmin injected in the eye and then incubated, which is the  
10 exact same method claimed by the applicant. The only difference is the dose  
11 size.

12 "The fact that both references teach plasmin injected into the eye and then  
13 incubated would cause some form of liquefaction. The examiner agrees that  
14 the prior art references never disclosed complete liquefaction of the vitreous  
15 of the eye. However, both references disclose some type of liquefaction."  
16 So there's sort of a number of things going on in that statement. You know,  
17 the dose size is admitted.

18 There's somewhat of a contradictory statement initially in this which says  
19 that the Examiner believes that the prior references teach .4 and yet  
20 subsequently he says the only difference is the dose size.

21 You know, he's basically made a finding that complete liquefaction is not  
22 taught in the prior art. Liquefaction in the context of the claims is really the  
23 ability to draw it out, to suction it through a small gauge needle without  
24 mechanical additions or efforts within the eye.

25 JUDGE KERINS: And thus that requires complete liquefaction.

1 MR. GOLDSTEIN: Exactly. In other words, going back to the jello  
2 analogy -- if you try to pull jello through a straw, at some point you're going  
3 to have trouble. So the solution medically is they go to a larger and larger  
4 bore needle, which causes more and more complications, more and more  
5 trauma to the eye.

6 The idea is to use a very small needle and, practically, to get that material  
7 through a smaller bore, it has to be liquefied.

8 JUDGE O'NEILL: So are you saying a person of ordinary skill in the art  
9 when interpreting the claim would understand a liquefied vitreous as a  
10 completely --

11 MR. GOLDSTEIN: As one that can be suctioned through a small-bore  
12 needle. I think that's a practical test in the field.

13 The other reference, you know, I don't think it's relevant. It's not of record  
14 with respect to the independent claims. There they did note some  
15 liquefaction, but it was so inconsistent that it didn't do them any good.

16 There was no value in doing it.

17 So the idea of starting a procedure with a small bore needle put into the eye  
18 to withdraw liquefied vitreous, and then saying, oh, it's clogged, we have to  
19 withdraw the small needle and now put in a large needle, surgically is not  
20 acceptable. You're increasing the trauma to the eye by having to replace the  
21 needle instead of the purpose of the invention which is less trauma, less  
22 invasion of the eye.

23 JUDGE KERINS: Do you have anything further?

24 JUDGE MCCARTHY: No.

25 JUDGE O'NEILL: No.

26 JUDGE KERINS: Thank you very much for your time.

1 MR. GOLDSTEIN: Thank you.

2 Whereupon, the proceeding at 1:33 p.m. was concluded.

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